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(54) Title: HORMONE REPLACEMENT FOR BREAST CANCER PATIENTS

(57) Abstract

Disclosed is a method of androgen replacement therapy to maintain or restore a woman's physiologic normality, including her bone density, vasomoter stability, sexual function, and energy. Also described is a method of treating or preventing osteoporosis in women. A woman is administered pharmaceutical compositions, comprising a non–aromatizable androgen, without estradiol or any estrogenic compound, by a route other than the digestive tract, such that 5 to 500 micrograms of the non–aromatizable androgen is administered daily. Pharmaceutical compositions for delivering a non–aromatizable androgen to a woman at higher than normal risk of breast cancer or endometrial cancer, are formulated to deliver an effective dose transdermally, transmucosally or by any delivery route, except the digestive tract. Non–aromatizable androgens that are contemplated include, but are not limited to, methyltestosterone, 17–alpha–methyl–19–nor–testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testolactone. But also contemplated amoung useful non–aromatizable androgens are androgenic progestins, including desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel. The absence from these compositions of estradiol, or any estrogenic compound, such as testosterone, avoids the estrogen exposure which increases the cancer risk. Androgen delivery other than by ingestion permits lower effective doses and thus lowers the risk of virilizing effects and potential liver toxicity than previously available androgen replacement preparations.

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HORMONE REPLACEMENT FOR BREAST CANCER PATIENTS

BACKGROUND OF THE INVENTION

Throughout this application various applications are referenced within parentheses. The disclosures of these publications in their entireties are hereby incorporated by reference in this application in order to more fully describe the state of the art to which this invention pertains.

1. FIELD OF THE INVENTION

This invention relates to the medical arts. In particular, it relates to a method of replacing androgen in a woman and a pharmaceutical composition useful therefor.

2. DISCUSSION OF THE RELATED ART

Women experiencing ovarian hormone deficiency resulting from natural menopause or surgical removal of the uterus and/or ovaries, are at higher than normal risk for atherosclerotic cardiovascular disease and osteoporosis. Chemotherapy used to treat cancer in women may also cause ovarian failure, increasing their risk for these conditions. Cardiovascular disease is the leading cause of death in women, accounting for 36% of all deaths and killing approximately 380,000 women each year. Osteoporosis, a loss of bone density and strength, is a serious condition affecting one-third to one-half of postmenopausal women. Nearly one-third of women over 65 will suffer at least one vertebral fracture as a result of osteoporosis; fractures of other weight-bearing bones are also common. In addition, many postmenopausal women report reduced libido and sexual functioning.

Estrogen replacement therapy (ERT) has long been used to prevent cardiovascular disease and osteoporosis in postmenopausal women and thus extend their life expectancy. However, ERT has been associated with an increased risk of cancers of the breast and endometrium, thromboembolic disease, gall bladder disease, and, in some cases, idiosyncratic increases in blood pressure, hypercalcemia, hypercoagulability, and hypertriglyceridemia.

Therapeutic combinations of hormones have been useful to reduce the cancer risk associated with ERT. For example, progestin has been co-administered with estrogen to prevent endometrial hyperplasia and carcinoma, but this combination has disadvantages associated with continuing menstrual cycling and symptoms such as cyclic depression, breast tenderness, and other symptoms resembling premenstrual syndrome. A combination of

estrogen and phytoestrogen reduces the risk of cardiovascular disease and osteoporosis (Hughes *et al.*, U.S. Pat. No. 5,516,528), while avoiding these progestin-associated side effects.

Combined estrogen-androgen replacement therapy also may have advantages over ERT alone for women suffering a deficiency of ovarian hormones. Male hormone, or androgen, such as testosterone, is produced by a woman's healthy ovary, albeit the serum levels of androgen in women are normally much lower than those found in men. In women, androgen plays a role in promoting cardiovascular health (P.M. Sarrel, *Cardiovascular Aspects of Androgens in Women*, Sem. Reprod. Endocrinol. 16(2):121-27 [1998]), in preventing osteoporosis (Kaunitz, *The Role of Androgens in Menopausal Hormonal Replacement*, Menopause and Hormone Replacement Therapy 26(2):391-97 [1997]; Hughes *et al.*, *Combined Pharmaceutical Estrogen-Androgen-Progestin Oral Contraceptive*, U.S. Pat. No. 5,770,226), in maintaining sexual drive and function (J.K. Warnock *et al.*, *Female Hypoactive Sexual Desire Disorder Due to Androgen Deficiency*, Psychopharmacology Bulletin 33(4):761-66 [1997]), and in enhancing women's general energy level and sense of well-being. (M.J. Rosenberg *et al.*, *Estrogen-Androgen for Hormone Replacement*, J. Reprod. Med. 42(7):394-404 [1997]). In one study, testosterone replacement therapy also led to increased body weight and improved quality of life for women suffering from AIDS wasting. (K. Miller *et al.*, *Transdermal Testosterone Administration in Women with Acquired Immunodeficiency Syndrome Wasting: A Pilot Study*, J. Clin. Endocrinol. Metab. 85(8):2717-25 [1998]).

Spicer *et al.* (*Methods And Formulations For Use In Inhibiting Conception and In Treating Benign Gynecological Disorders*, U.S. Pat. No. 5,340,584) and Pike *et al.* (*Methods And Formulations For Use In Treating Benign Gynecological Disorders*, U.S. Pat. No. 5,340,585; *Methods And Formulations For Use In Treating Oophorectomized Women*, 5,340,586) taught therapeutic combinations of gonadotropin hormone releasing hormone with estrogen and/or an androgen for naturally and surgically menopausal women; they also taught estrogenic/androgenic combinations. Ebert *et al.* (*Methods for providing testosterone and optionally estrogen replacement therapy to women*, U.S. Pat. No. 5,460,820) and Venkateshwaran *et al.* (*Transdermal drug delivery matrix for coadministering estradiol and another steroid*, U.S. Pat. No. 5,783,208) taught a method and patches for transdermal delivery to women of estrogen combined with testosterone, an aromatizable androgen. Commercial preparations combining estrogen and methyltestosterone have been marketed in

the United States since 1964 for the treatment of moderate-to-severe vasomotor instability ("hot flashes"), and other menopausal symptoms in patients whose symptoms have not been relieved by ERT. (E. Phillips and C. Bauman, *Safety Surveillance of Esterified Estrogens-Methyltestosterone (Estratest® and Estratest® HS) Replacement Therapy in The United States*, Clin. Ther. 19(5):1070-84 [1997]). These pharmaceutical preparations are formulated for oral delivery, as in Estratest® and Estratest® HS (Solvay Pharmaceuticals, Inc., Marietta, GA), characteristically containing 0.625 to 1.25 mg of esterified estrogens and 1.25 to 2.5 mg of methyltestosterone in a daily dose. Methyltestosterone, a synthetic non-aromatizable androgen, is a lipophilic compound similar to testosterone in its physical properties, including water solubility. Methyltestosterone administered orally, is known to be about three to four times more androgenically potent than testosterone. (R.V. Quincey and C.H. Gray, *The metabolism of [1,2-^{3}H]17alpha-methyltestosterone in human subjects*, J. Endocrinol. 37:37-55 [1967]). Sublingual (transmucosal) delivery systems for administering greater than 5 mg doses of methyltestosterone to hypogonadal men are also known. (D. Alkalay *et al.*, *Sublingual and Oral Administration of Methyltestosterone. A comparison of Drug Bioavailability*, J. Clin. Pharmacol. 13(4):142-51[1973]).

Other noncombined androgen preparations are available in the form of oral micronized testosterone, testosterone creams, gels, transdermal patches, injectable testosterone crystals or implantable testosterone pellets for men or women. (Ebert *et al.*, *Method and device for transdermally administering testosterone across nonscrotal skin at therapeutically effective levels*, U.S. Pat. No. 5,152,997; Ebert *et al.*, *Methods for providing testosterone and optionally estrogen replacement therapy to women*, U.S. Pat. No. 5,460,820; Sidman, *Biodegradable, implantable drug delivery device, and process for preparing and using the same*, U.S. Pat. No. 4,351,337; Feijen, *Biodegradable hydrogel matrices for the controlled release of pharmacologically active agents*, U.S. Pat. No. 4,925,677).

Unfortunately, for women at higher than normal risk of breast cancer or endometrial cancer, ERT or combined estrogen-androgen replacement therapy may be an unacceptably risky treatment option. Women at increased risk may include those already diagnosed with a cancer of the breast or the endometrium, those who have successfully survived treatment for such cancer, or those with a known family history of such cancers. These women may choose to forego the physiologic benefits of ovarian hormone replacement therapy due to the carcinogenic- and other hazards posed by estrogen. Women treated with estrogen and/or androgen replacement preparations containing an aromatizable androgen, such as

testosterone, receive an even higher estrogen exposure. This is because testosterone is physiologically convertible to estrogen by way of an aromatase-mediated biochemical pathway. (D.F. Dimick *et al.*, *A comparative study of the metabolic fate of testosterone, 17a-methyl-testosterone, 19-nor-testosterone, 17a-methyl-19-nor-testosterone and 17a-methyl--estr-5(10)-ene-17-b-OL-3-one ion normal males*, Clin. Chim. Acta 6:63-67 [1961]; R.V. Quincey and C.H. Gray [1967]). Consequently, testosterone and its precursor androstenedione are also associated with increased breast cancer risk. (A. Zeleniuch-Jacotte *et al.*, *Relation of Serum Levels of Testosterone and Dehydroepiandrosterone Sulfate to Risk of Breast Cancer in Postmenopausal Women*, Am. J. Epidemiol. 145(11):1030-38 [1997]; F. Berrino *et al.*, *Serum Sex Hormone Levels After Menopause and Subsequent Breast Cancer*, J. Natl. Cancer Inst. 88(5):291-96 [1996]; J.F. Dorgan *et al.*, *Relation of Prediagnostic Serum Estrogen and Androgen Levels to Breast Cancer Risk*, Cancer Epidemiol., Biomarkers Prevent. 5(7):533-39 [1996]; D. Wysowski *et al.*, *Sex Hormone Levels in Serum in Relation to the Development of Breast Cancer*, Am. J. Epidemiol. 126(5):791-99 [1987]). Aromatase inhibitors, such as 4-OH-androstenedione, the active ingredient in LENTARON®, have been used clinically in breast cancer therapy. (C. Rose, *Proper Sequence of Endocrine Therapies in Advanced Breat Cancer*, Acta Oncol. 34(55):44-49 [1996]).

In addition, while estrogen-androgen replacement therapy has given relief from menopausal symptoms to many women, a significant number have also experienced some adverse side effects associated with the relatively high doses of non-aromatizable androgen present in the oral preparations heretofore available. These adverse side effects include alopecia (hair loss from the scalp and elsewhere), acne, hirsutism, lowering of the voice, or substantial enlargement of the clitoris (Philips and Bauman [1997]; S.M. Slayden, *Risks of Menopausal Androgen Supplementation*, Sem. Reprod. Endocrinol. 16(2):145-52 [1998]). These virilizing effects are typically dose- and duration-dependent, and they sometimes result at typical oral doses after typical replacement periods (greater than 6 months). (M.M. Gelfand and B. Wiita, *Androgen and Estrogen-Androgen Hormone Replacement Therapy: A review of the Safety Literature*, Clin. Ther. 19(3):383-404 [1997]).

Methyltestosterone at higher doses prescribed to men (40 mg/day) is linked to significantly decreased serum levels of high-density lipoprotein cholesterol and a greater risk of coronary artery disease. (K.E. Friedl *et al.*, *High-density Lipoprotein Cholesterol Is Not Decreased if an Aromatizable Androgen is Administered*, Metabolism 39:69-74 [1990]). More significant for women are reports of liver toxicity (hepatotoxicity) when estrogen and

androgens, such as methyltestosterone, are delivered by way of the digestive tract. (Stevenson *et al., Oral Versus Transdermal Hormone Replacement Therapy*, Int. J. Fertil. 38:30-35 [1993]). Liver toxicity from methyltestosterone has been noted primarily at doses above 10 mg given to hypogonadal men and female-to-male transsexuals, and is not clearly a risk at lower doses. (G.L. Foss and S.L. Simpson, *Oral Methyltestosterone and Jaundice*, Br. Med. J. 1:259-63 [1959]; Warnock [1997]; Kaunitz [1997]; B. Ettinger and B. Fireman, *Estrogen-androgen hepatotoxicity?*, Am J. Obstet. Gynecol. 178(3) 627-28 [1998]). However, individual women's sensitivities to hepatotoxic effects of methyltestosterone may vary considerably, and there is a potential for increased risk of liver damage from alkylated steroid hormones, such as methyltestosterone, even at doses now commonly prescribed to women. (Gelfand and Wiita [1997]; Ettinger and Fireman [1998]).

SUMMARY OF THE INVENTION

The present invention provides methods and pharmaceutical compositions for administering an effective dose of a non-aromatizable androgen to a woman, which is intended to maintain her physiologic normality, while avoiding the estrogen exposure from currently available hormone replacement methods and preparations. The present invention thus avoids the higher risks of breast- and endometrial cancer associated with estrogen and other estrogenic compounds, such as aromatizable androgens, including testosterone. In the present invention, delivery of a non-aromatizable androgen is by a route other than the woman's digestive tract. This feature of the present invention, provides lower effective doses and thus a lower risk of virilizing effects and potential liver toxicity, associated with previously available androgen preparations.

The method of the present invention includes administering to a woman a composition comprising a non-aromatizable androgen, but without an estrogen or any estrogenic compound. Forms of estrogen, such as the major female hormone estradiol, are intentionally lacking from the pharmaceutical composition of this invention, because estrogen is linked to an increased risk of cancers of the breast and endometrium. Estrogenic compounds, i.e., compounds that lead to the production of estrogen, are also lacking from the composition of the present invention. Estrogenic compounds can include gonadotropins, that hormonally stimulate endogenous estrogen production, and aromatizable androgens, such as androstenedione and testosterone, which are precursor molecules physiologically convertible to estradiol. The absence of estrogen and estrogenic compounds from the composition to be

administered in the present methods thus gives to those menopausal women concerned about ERT-related cancer risks a therapeutic option to protect against the occurrence and severity of osteoporosis, to relieve vasomotor instability, and to improve sexual function and energy.

The present invention also relates to pharmaceutical compositions, for the treatment of women, that include a non-aromatizable androgen deliverable by a route other than the digestive tract. The non-aromatizable androgen contemplated in the present invention encompasses androgenic compounds, whether natural or synthetic, that are not metabolizable to a biologically active form of estrogen. Naturally occurring non-aromatizable androgens include, but are not limited to, 5-alpha reduced dihydroxytestosterone. Examples of synthetic non-aromatizable androgens include, but are not limited to, 17-alkylated androgens, such as methyltestosterone (17-alpha-methyl-testosterone), and 17-alpha-methyl-19-nor-testosterone, or other 19-nor-testosterone derivatives. Because the non-aromatizable androgen of the pharmaceutical composition of the present invention is not substantially metabolizable to a bioactive form of estrogen before it is cleared from a woman's body, there is a reduced risk of carcinogenesis in breast and endometrial tissue compared to previously available ERT and combined hormone replacement preparations.

The present invention also relates to a method of delivering, by a route other than the digestive tract, an effective dose of a non-aromatizable androgen to a woman at higher than normal risk of breast cancer or endometrial cancer. Patients with cancers of the breast or endometrium, breast cancer survivors, and other women at higher than normal risk of breast cancer are generally denied the use of estrogens for the management of menopausal symptoms and sexual dysfunction resulting from their natural menopausal state or from chemotherapy-induced ovarian failure. The methods of the present invention, including a method of treating or preventing osteoporosis, gives these women, too, an opportunity to enjoy the important bone-protective benefits of hormone replacement therapy, as well as relief from vasomotor instability, and improved sexual functioning and energy levels. In addition, breast cancer patients, who not uncommonly experience wasting during the course of treatment, may benefit from enhancements in body weight, muscle strength, and energy resulting from androgen replacement therapy.

In practicing the methods of the present invention, the effective dose of non-aromatizable androgen delivered to a woman is lower than that allowed by methods heretofore, because the present invention is directed to compositions formulated to deliver a non-aromatizable androgen by any pharmaceutically acceptable delivery system other than

ingestion. Thus in practicing the present methods, a daily dose in the range of 5 to 500 micrograms of non-aromatizable androgen is contemplated, to be administered by a route other than the digestive tract, but not limited to, adhesive patches, topical creams or ointments for transdermal delivery; injection; implant; transmucosal delivery matrices or vaginal suppositories or gels. Within the dose range of the present invention, the effective dose for any individual woman may vary and can be determined by her physician by routine calibration to her individual needs under careful treatment monitoring.

The advantage of administering a non-aromatizable androgen within the dose range of the present invention is a lower risk of virilizing effects and other adverse effects sometimes seen in patients receiving the higher doses of methyltestosterone in previously available preparations. The potential for hepatotoxic effects is similarly reduced by the lower doses provided by the present invention.

These and other advantages and features of the present invention will be described more fully in a detailed description of the preferred embodiments which follows.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides methods of androgen replacement therapy and pharmaceutical compositions for delivering, by a route other than the digestive tract, an effective dose of a non-aromatizable androgen to a woman, which is intended to maintain or restore her physiologic normality, while avoiding the estrogen exposure from previously available hormone replacement methods and preparations. The present invention thus avoids the higher risks of breast cancer and endometrial cancer associated with the administration of estrogen and other estrogenic compounds, such as aromatizable androgens, including testosterone. In the present invention, administration of a non-aromatizable androgen is by a delivery route other than the digestive tract. This permits lower effective doses and thus lowers the risk of virilizing effects and potential liver toxicity, which are associated with previously available androgen preparations.

The present invention is directed to methods of treating osteoporosis in a woman. One of the principal benefits of the methods and compositions of the present invention to menopausal women and to women at higher than normal risk for breast and endometrial cancers is in stabilizing or improving bone density. While the present invention does not propose a precise mechanism of action, abundant evidence supports the well-established conclusion that androgens play a role in building and maintaining bone in women as well as

in men. (Rosenberg *et al.* [1997]). Androgens are known to stimulate osteoblast differentiation and proliferation, (Kasperk *et al., Studies of the mechanism by which androgens enhance mitogenesis and differentiation in bone*, J. Clin. Endocrinol. Metab. 71:1322-29 [1990]). Androgen receptors have been identified in osteoblast-like cells (Colvard *et al., Identification of androgen receptors in normal human osteoblast-like cells*, Proc. Natl. Acad. Sci. USA 86:854-57 [1989]; Wiren *et al., Homologous regulation of the androgen receptor in human osteoblastic cells*, J. Bone Miner. Res., 10(Suppl. 1):S494 [1995]), and they may modulate calcium channels in bone cells. (Takeuchi and Guggino, *24R,25-$(OH)_2$ Vitamin D3 inhibits 1 alpha,25-$(OH)_2$ Vitamin D3 and testosterone potentiation of calcium channels in osteosarcoma cells*, J. Biol. Chem. 271(52):33335-43 [1996]). Androgen replacement using the methods and compositions of the present invention will contribute to the stabilization or improvement of a woman's bone density, which is among the physiologic conditions that the methods of the present invention are intended to maintain or restore to physiologic normality.

The methods of the present invention are also contemplated to improve vasomoter stability, libido, sexual functioning, and a general feeling of well-being in a woman to whom an effective dose of a non-aromatizable androgen is administered. These, too, are among the physiologic conditions that the methods of the present invention are intended to maintain or restore to physiologic normality.

The present invention also relates to a method of androgen replacement therapy for a woman and a method of treating or preventing osteoporosis, and compositions for administering, by a delivery route other than the digestive tract, an effective dose of a non-aromatizable androgen to a woman at higher than normal risk of breast cancer or endometrial cancer. Women are contemplated who have an increased risk relative to the general population of women. It is well known that women at increased risk may include those already diagnosed with a cancer of the breast, ovary or endometrium, or those who have successfully survived treatment for such cancer, or those with a known family history of such cancers. For example, the skilled practitioner will be able to identify women who would benefit from androgen replacement therapy, but who are at an increased risk of breast cancer, based on a first degree family history of breast, ovarian, endometrial, or prostatic cancer. (E.B Claus *et al., The calculation of breast cancer risk for women with a first degree family history of ovarian cancer*, Breast Cancer Res. Treat. 28(2):115-20 [1993]; N. Eby *et al., Familial risk and genetic susceptibility for breast cancer*, Cancer Causes Control 5(5):458-70 [1994]; F.

Parazinni *et al.*, *Family history of breast, ovarian and endometrial cancer and risk of breast cancer*, Int. J. Epidemiol. 22(4):614-18 [1993]; D.E. Anderson and M.D. Badzioch, *Familial effects of prostate and other cancers on lifetime breast cancer risk*, Breast Cancer Res. Treat. 28(2):107-13 [1993]; P.J. McCahy *et al.*, *Breast and prostate cancer in the relatives of men with prostate cancers*, Br. J. Urol. 78(4):552-56 [1996]). Also, a higher risk of breast cancer may exist in women with such a family history, when they have a high waist-to-hip ratio of fat distribution. (T.A. Sellers et al., *Association of body fat distribution and familial histories of breast and ovarian cancer with risk of postmenopausal breast cancer*, Am. J. Epidemiol. 138(10):799-803 [1993]).

Women who themselves have had a primary ovarian or uterine cancer have substantially increased risk for developing a secondary breast cancer; similarly, primary breast cancer is a significant risk factor for secondary endometrial cancer. (S.A. Narod, *Genetics of breast and ovarian cancer*, Br. Med. Bull. 50(3):656-76 [1994]); J.B. Bokhman and S.J. Maximov, *Relative risk of development and active detection of primary multiple endometrial, breast and ovarian cancer*, Eur. J. Gynaecol. Oncol. 14(2):114-118 [1993]; S.A. Auranen *et al.*, *Primary breast cancer and colon cancer associated with endometrial or ovarian cancer*, Ann. Chir. Gynaecol. Suppl. 208:5-9 [1994]). Clinical manifestations, such as endometrial hyperplasia or breast gross cystic disease may be additional indicators of higher risk.

Also, for purposes of the present invention, women at higher than normal risk, include women identified as having genetic markers associated with greater risk of breast cancer or endometrial cancer. Genetic markers linked with increased breast cancer or endometrial cancer risk include, but are not limited to, markers of BRCA1 (White *et al.*, *Susceptibility mutation for breast and ovarian cancer*, U.S. Pat. No. 5,756,294), Mat-8 (Morrison *et al.*, *DNA encoding Mat-8*, U.S. Pat. No. 5,728,579), c-erbB-2/neu, FGF-3/INT-2 (M. Estellar *et al.*, *Detection of c-erbB/neu and fibroblast growth factor-3/INT-2 but not epidermal growth factor receptor gene amplification in endometrial cancer by differential polymerase chain reaction*, Cancer 75(8):2139-46 [1995]), or shortened telomere length (T. Levy *et al.*, *Telomere length in human white blood cells remains constant with age and is shorter in breast cancer patients*, Anticancer Res. 18(3A):1345-49 [1998]). These and other markers may be used by the skilled practitioner to identify women at higher risk of breast or endometrial cancers.

Techniques of assessing higher risk are readily available. These may involve assays for breast cancer-associated genetic markers, as above (Kieback, *Methods for diagnosing an*

increased risk for breast cancer, U.S. pat. Nos. 5,645,995 and 5683,885), or for breast cancer-associated proteins or glycoproteins (Morrison *et al.*, U.S. Pat. No. 5,728,579; Quay *et al.*, *Methods and kits for obtaining and assaying mammary fluid samples for breast diseases, including cancer*, U.S. Pat. No. 5,798,266; Haagensen *et al.*, *Method of determining the risk of breast cancer development*, U.S. Pat. No. 5,648,224; Manning *et al.*, *Methods for predicting the behavior of breast tumours*, U.S. Pat. No. 5,693,465; Olsson, *Prognostic markers in human breast cancer*, U.S. Pat. No. 5,415,996; Feller *et al.*, *Breast cancer diagnostic blood test*, U.S. Pat. No. 4,657,851; Bartorelli *et al.*, *Breast cancer antigens*, U.S. Pat. No. 4,383,985; Smith *et al.*, *Detecting neoplastic epithelial cells by detecting thioesterase II marker*, U.S. Pat. No. 4,529,693), or assays, for example, of chloride ion in breast cyst fluid (Fleisher *et al.*, *Breast cyst fluid screening method for cancer risk assessment*, U.S. Pat No. 4,695,471). This list is not exhaustive, but merely illustrates that means of risk assessment for breast cancer and endometrial cancer are known and available to the practitioner.

The methods and compositions of the present invention employ a non-aromatizable androgen. An "androgen" is a male sex hormone, for example testosterone or dihydrotestosterone, or any other compound that binds to androgen receptors or binding sites on any of a woman's cell surfaces, so as to produce within the cell bearing such a receptor, a hormonal cascade with a physiologic effect similar to that caused by the binding of a male sex hormone to such an androgen receptor.

The skilled artisan will be aware that androgen receptors are found in numerous tissues in women, including tissues of the skin, bone, larynx, breast, endometrium, and myometrium. Androgen receptors are also concentrated in the normal female brain; an androgen deficiency results in a global loss of sexual desire, decreased sensitivity to sexual stimulation in the nipples and in the clitoris, decreased arousability and capacity for orgasm, loss of muscle tone, diminished vital energy, thinning and loss of pubic hair, and dry skin. (Warnock *et al.* [1997]). Along with a woman's bone density, these are among the physiologic conditions that the methods of the present invention are intended to maintain or restore to physiologic normality.

"Non-aromatizable androgen" means an androgen that is not convertible by an aromatase to an estrogen or estrogen precursor. The non-aromatizable androgen contemplated in the present invention encompasses androgenic compounds, whether natural or synthetic, that are not metabolizable to a biologically active form of estrogen. Androgens useful in practicing the methods of the present invention, or in the pharmaceutical compositions of the

present invention, include naturally occurring or synthetic non-aromatizable androgens, including, but not limited to, 17-alkylated androgens and 19-nor-testosterone derivatives.

A preferred embodiment employs a naturally occurring non-aromatizable androgen, such as 5-alpha reduced dihydrotestosterone. Other preferred embodiments employ synthetic non-aromatizable androgens, including, but not limited to, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, or the aromatase inhibitor testolactone.

A most preferred embodiment employs methyltestosterone (17-alpha-methyl-testosterone). Androgenic progestins are a category of compounds that would be "non-aromatizable androgens" for purposes of the present invention, because they competitively bind to androgen receptors with physiologic effect. Androgenic progestins that could be employed in a preferred embodiment as a non-aromatizable androgen include, but are not limited to, desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, or ethynodiol diacetate. A most preferred embodiment employing an androgenic progestin, would use levonorgestrel.

An "effective dose" means a dose of non-aromatizable androgen that will produce stabilization or improvement in the physiologic condition of an individual woman needing androgen replacement therapy. This stabilization or improvement is what is meant by "physiologic normality" for purposes of the present invention. The skilled practitioner will readily apprehend that the tests appropriately employed to determine an effective dose will depend on the individual clinical needs of each patient. The effective dose for each woman will depend upon the physiologic reactions of the patient to whom the compositions of the present invention are administered, and the patients reactions will be monitored by the prescribing physician. It is contemplated that the pharmaceutical compositions of the present invention may be formulated and manufactured at more than one concentration of non-aromatizable androgen, such that modular increments of non-aromatizable androgen may be easily administered within the dose range of 5 to 500 micrograms per day. This will give the physician more choices in finding the best effective dose for each patient.

Stabilization or improvement in the physiologic condition of an individual woman may be determined by a practitioner using any appropriate clinical, biochemical, or physiologic measurements, screenings, assays, evaluations, monitoring, or tests known in the art. For example, bone density monitoring may be carried out by conventional methods known to one skilled in the art, such as dual photon absorptiometry. (E.g., J.C. Stevenson *et*

al., Lancet 336:265-69 [1990]). Libido, sexual functioning, and general energy level may be evaluated using standard gynecological measurements or observations, or by query or questionnaire directed to the patient. (E.g., Warnock *et al.* [1997]). The physician may, optionally, monitor the patient's serum androgen levels over a period of months in order to facilitate the determination of a suitable effective dose of non-aromatizable androgen. Once the patient is on long-term androgen therapy, routine monitoring of serum androgen may be discontinued, absent any change in the patient's condition or the appearance of androgenic side effects. Androgenic side effects may be experienced by patients at higher doses. Early side effects that are easily recognized and detected by the patient and physician include acne, and hirsutism, both of which imply that dose reduction should be considered. These symptoms are readily reversible if detected early. Advanced hirsutism, voice changes, changes in muscle mass, or clitoromegaly are more advanced androgen excess side effects that are avoidable by response to early detection and adjustment of dosages accordingly.

For purposes of the present invention, "administering" means giving, providing, dispensing, prescribing, furnishing, treating with, taking or applying a composition of the present invention.

"Delivery route other than the digestive tract" means first entry of the non-aromatizable androgen into the blood stream of a woman by any route, device, method or mechanism that does not require the non-aromatizable androgen to initially pass through any of the organs of the digestive tract before entering the blood stream. The organs of the digestive tract include the esophagus, stomach, large intestine, small intestine, or rectum. For the purposes of the present invention, entry through the mucosa or epithelium of the mouth, including the sublingual epithelium, is delivery by a route other than the digestive tract. Other delivery routes that are contemplated by the present invention as "other than the digestive tract" include, but are not limited to, adhesive patches, topical creams or ointments for transdermal delivery; injection; implant; transmucosal delivery matrices or vaginal suppositories or gels. It is contemplated that the compositions of the present invention are formulated to deliver an effective dose of an aromatizable androgen by these or any other pharmaceutically acceptable non-ingestive delivery system.

Specific embodiments of delivery routes and pharmaceutically acceptable delivery systems that could be employed by one of skill in the art in practicing the methods and compositions of the present invention are now exemplified. The following are presented merely to illustrate and in no way to limit the possible delivery means contemplated.

A preferred embodiment of the compositions of the present invention is a topical ointment or gel to be applied to the skin. In this embodiment, a composition of the present invention comprises, a non-aromatizable androgen, in a pharmaceutically acceptable delivery system comprising a permeation or penetration enhancer, such as polyethylene glycol monolaurate, dimethyl sulfoxide, N-vinyl-2-pyrrolidone, N-(2-hydroxyethyl)-pyrrolidone, or 3-hydroxy-N-methyl-2-pyrrolidone. A variety of conventional thickeners, such as alginate, xanthan gum, or petrolatum, may also be employed in the composition.

Another preferred embodiment of the compositions of the present invention is a preparation for transmucosal delivery of a non-aromatizable androgen. A variety of pharmaceutically acceptable systems for transmucosal delivery of therapeutic agents are known in the art and are compatible with the practice of the present invention. (Heiber *et al.*, *Transmucosal delivery of macromolecular drugs*, U.S. Pat. Nos. 5,346,701 and 5,516,523; Longenecker *et al.*, *Transmembrane formulations for drug administration*, U.S. Pat. No. 4,994,439). Transmucosal delivery devices may be in free form, such as a cream, gel, or ointment, or may comprise a determinate form such as a tablet, patch, or troche. For example, delivery of a non-aromatizable androgen may be via a transmucosal delivery system comprising a laminated composite of, for example, an adhesive layer, a backing layer, an androgen-permeable membrane defining a reservoir containing a non-aromatizable androgen, a peel seal disc underlying the membrane, one or more heat seals, and a removable release liner. (Ebert *et al.*, *Transdermal delivery system with adhesive overlay and peel seal disc*, U.S. Pat No. 5,662,925; Chang *et al.*, *Device for administering an active agent to the skin or mucosa*, U.S. Pat. Nos. 4,849,224 and 4,983,395).

Alternatively, a tablet or patch for delivery through the oral mucosa may comprise an inner layer containing the therapeutic agent of choice, a permeation enhancer, such as a bile salt or fusidate, and a hydrophilic polymer, such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, dextran, pectin, polyvinyl pyrrolidone, starch, gelatin, or any of a number of other polymers known to be useful for this purpose. This inner layer may have one surface adapted to contact and adhere to the moist mucosal tissue of the oral cavity and may have an opposing surface adhering to an overlying non-adhesive inert layer. Optionally, such a transmucosal delivery system may be in the form of a bilayer tablet, in which the inner layer also contains additional binding agents, flavoring agents, or fillers. Some useful systems employ a non-ionic detergent along with a permeation enhancer. These examples are merely illustrative of available transmucosal delivery technology and are not

limiting of the present invention.

Another preferred embodiment of the compositions of the present invention is a gel for delivery of a non-aromatizable androgen via the vaginal mucosa, similar to gels commonly used for the delivery of progesterone, other female hormones, or various therapeutic agents. Hydrogel matrices are known for this purpose. (Feijen, *Biodegradable hydrogel matrices for the controlled release of pharmacologically active agents*, U.S. Pat. No. 4,925,677). Such biodegradable gel matrices may be formed, for example, by cross-linking a proteinaceous component and a polysaccharide or mucopolysaccharide component, then loading with a non-aromatizable androgen to be delivered.

Another preferred embodiment of the compositions of the present invention is the delivery of a non-aromatizable androgen via a biodegradable matrix implanted within the body or under the skin of a woman. The implant matrix may be a hydrogel similar to those described above. Alternatively, it may be formed from a poly-alpha-amino acid component. (Sidman, *Biodegradable, implantable drug delivery device, and process for preparing and using same*, U.S. Pat. No. 4,351,337).

A most preferred embodiment of the composition of the present invention is a transdermal delivery system of a kind known in the art for delivering drugs or hormones, including aromatizable androgens. Transdermal delivery systems of the most preferred embodiment may be of any number of varieties known in the art. For example, delivery of a non-aromatizable androgen may be via a delivery system comprising a laminated composite of an adhesive layer, a backing layer, an androgen-permeable membrane defining a reservoir containing a non-aromatizable androgen, a peel seal disc underlying the membrane, one or more heat seals, and a removable release liner. (Ebert *et al.*, *Transdermal delivery system with adhesive overlay and peel seal disc*, U.S. Pat No. 5,662,925; Chang *et al.*, *Device for administering an active agent to the skin or mucosa*, U.S. Pat. Nos. 4,849,224 and 4,983,395).

Alternatively, a transdermal delivery device of the most preferred embodiment may be a matrix type transdermal patch. (Chien *et al.*, *Transdermal estrogen/progestin dosage unit, system and process*, U.S. Pat. Nos. 4,906,169 and 5,023,084; Cleary *et al.*, *Diffusion matrix for transdermal drug administration and transdermal drug delivery devices including same*, U.S. Pat. No. 4,911,916; Teillaud *et al.*, *EVA-based transdermal matrix system for the administration of an estrogen and/or a progestogen*, U.S. Pat. No. 5.605,702; Venkateshwaran *et al.*, *Transdermal drug delivery matrix for coadministering estradiol and*

another steroid, U.S. Pat. No. 5,783,208; Ebert *et al.*, *Methods for providing testosterone and optionally estrogen replacement therapy to women*, U.S. Pat. No. 5,460,820). The matrix of the patch may comprise a basal support layer, such as an acrylic or ethylene/vinyl acetate copolymer or a polyurethane foam or cellulosic material, and an adhesive, such as, but not limited to, polysiloxane. In the compositions of the present invention, the polymer matrix also contains a non-aromatizable androgen, without any estrogen or estrogenic compound, as described above, and optionally, a penetration-enhancing vehicle or carrier, such as N-vinyl-2-pyrrolidone, N-(2-hydroxyethyl)-pyrrolidone, or 3-hydroxy-N-methyl-2-pyrrolidone. The adhesive patch may be pressure-sensitive, to release the non-aromatizable androgen across the skin of the user when the patch matrix has been applied to her skin. The patch may optionally comprise an inert backing layer in addition to a matrix layer, or may comprise multiple dosage units or layers.

By avoiding delivery of a non-aromatizable androgen by way of the digestive tract, the present invention has the advantage of providing a lower effective dose than would be possible by ingestion. Before entering the blood stream, an ingested non-aromatizable androgen, for example, methyltestosterone, faces degradative processes associated with the digestive tract and hepatic enzymes. Therefore, in addition to a lower risk of virilizing side effects, one advantage of lowering the effective dose as much as possible is a lesser potential risk of liver toxicity.

While the invention has been described with reference to its preferred embodiments, it will be appreciated by those skilled in this art that variations may be made departing from the precise examples of the methods and compositions disclosed herein, which, nonetheless, embody the invention defined by the following claims.

CLAIMS

1. A method of androgen replacement therapy to maintain or restore a woman's physiologic normality, comprising:

administering to a woman, by a delivery route other than the digestive tract, 5 to 500 micrograms per day of a non-aromatizable androgen, without estradiol or any estrogenic compound, whereby the woman's physiologic normality is maintained or restored.

2. The method of Claim 1, wherein said non-aromatizable androgen is methyltestosterone.

3. The method of Claim 1, wherein said non-aromatizable androgen is selected from the group consisting of 17-alpha-methyl-testosterone, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testolactone.

4. The method of Claim 1, wherein said non-aromatizable androgen is 5-alpha reduced dihydrotestosterone.

5. The method of Claim 1, wherein said route is a transdermal delivery route.

6. The method of Claim 1, wherein said route is an injection or implant delivery route.

7. The method of Claim 1, wherein said route is a transmucosal delivery route.

8. The method of Claim 7, wherein said route is an oral mucosal delivery route.

9. The method of Claim 7, wherein said route is a vaginal mucosal delivery route.

10. The method of Claim 1, wherein said non-aromatizable androgen is an androgenic progestin selected from the group consisting of desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel.

11. The method of Claim 10, wherein said androgenic progestin is levonorgestrel.

12. A method of androgen replacement therapy for a woman at higher than normal risk of breast cancer or endometrial cancer, comprising:

administering to a woman at higher than normal risk of breast cancer or endometrial cancer, by a delivery route other than the digestive tract, 5 to 500 micrograms per day of a non-aromatizable androgen, without estradiol or any estrogenic compound, whereby the woman's physiologic normality is maintained or restored and her exposure to estrogen is minimized.

13. The method of Claim 12, wherein said non-aromatizable androgen is methyltestosterone.

14. The method of Claim 12, wherein said non-aromatizable androgen is selected from the group consisting of 17-alpha-methyl-testosterone, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testolactone.

15. The method of Claim 12, wherein said non-aromatizable androgen is 5-alpha reduced dihydrotestosterone.

16. The method of Claim 12, wherein said route is a transdermal delivery route.

17. The method of Claim 12, wherein said route is an injection or implant delivery route.

18. The method of Claim 12, wherein said route is a transmucosal delivery route.

19. The method of Claim 18, wherein said route is an oral mucosal delivery route.

20. The method of Claim 18, wherein said route is a vaginal mucosal delivery route.

21. The method of Claim 12, wherein said non-aromatizable androgen is an androgenic progestin selected from the group consisting of desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel.

22. The method of Claim 21, wherein said androgenic progestin is levonorgestrel.

23. A method of treating or preventing osteoporosis in a woman at higher than normal risk of breast cancer or endometrial cancer, comprising:

administering to a woman at higher than normal risk of breast cancer or endometrial cancer, by a route other than the digestive tract, 5 to 500 micrograms per day of a non-aromatizable androgen, without estradiol or any estrogenic compound, whereby the woman's bone density is stably maintained or improved and her exposure to estrogen is minimized.

24. The method of Claim 23, wherein said non-aromatizable androgen is methyltestosterone.

25. The method of Claim 23, wherein said non-aromatizable androgen is selected from the group consisting of 17-alpha-methyl-testosterone, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testolactone.

26. The method of Claim 23, wherein said non-aromatizable androgen is 5-alpha reduced dihydrotestosterone.

27. The method of Claim 23, wherein said route is a transdermal delivery route.

28. The method of Claim 23, wherein said route is an injection or implant delivery

route.

29. The method of Claim 23, wherein said route is a transmucosal delivery route.

30. The method of Claim 29, wherein said route is an oral mucosal delivery route.

31. The method of Claim 29, wherein said route is a vaginal mucosal delivery route.

32. The method of Claim 23, wherein said non-aromatizable androgen is an androgenic progestin selected from the group consisting of desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel.

33. The method of Claim 32, wherein said androgenic progestin is levonorgestrel.

34. A pharmaceutical composition for delivering androgen to a woman by a route other than her digestive tract, said composition comprising a non-aromatizable androgen, without estradiol or any estrogenic compound, in a pharmaceutically acceptable non-ingestive delivery system formulated to deliver 5 to 500 micrograms per day of said non-aromatizable androgen.

35. The pharmaceutical composition of Claim 34, wherein said non-aromatizable androgen is synthetic.

36. The pharmaceutical composition of Claim 34 wherein said non-aromatizable androgen is methyltestosterone.

37. The pharmaceutical composition of Claim 34, wherein said non-aromatizable androgen is selected from the group consisting of 17-alpha-methyl-testosterone, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testolactone.

38. The pharmaceutical composition of Claim 34, wherein said non-aromatizable androgen is 5-alpha reduced dihydrotestosterone.

39. The pharmaceutical composition of Claim 34, wherein said delivery system is a transdermal delivery system.

40. The pharmaceutical composition of Claim 39, wherein said delivery system comprises an adhesive patch.

41. The pharmaceutical composition of Claim 39, wherein said delivery system comprises a gel or cream.

42. The pharmaceutical composition of Claim 34, wherein said delivery system is an injection or implant delivery system.

43. The pharmaceutical composition of Claim 34, wherein said delivery system

is a transmucosal delivery system.

44. The pharmaceutical composition of Claim 43, wherein said delivery system is an oral transmucosal delivery system.

45. The pharmaceutical composition of Claim 43, wherein said delivery system is a vaginal transmucosal delivery system.

46. The pharmaceutical composition of Claim 34, wherein said non-aromatizable androgen is an androgenic progestin selected from the group consisting of desogestrel, norgestimate, norethindrone, norethinedrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel.

47. The pharmaceutical composition of Claim 36, capable of delivering a daily dose of methyltestosterone within the range of 5 to 500 micrograms.

48. A pharmaceutical composition for delivering a non-aromatizable androgen to a woman by a route other than her digestive tract, said composition comprising methyltestosterone deliverable at a daily dose of 5 to 500 micrograms per day, without estradiol or any estrogenic compound, in a pharmaceutically acceptable non-ingestive delivery system.

49. The pharmaceutical composition of Claim 48, wherein said delivery system is a transdermal delivery system.

50. The pharmaceutical composition of Claim 48, wherein said delivery system is a transmucosal delivery system.

51. The pharmaceutical composition of Claim 48, wherein said delivery system is an injection or implant delivery system.